

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Marked-up Version Showing Changes.**"

### REMARKS

Claims 1-7, and 9-19 are pending in the present application. The Examiner objected to the specification because the Brief Description of the Drawings refers to Figure 1. The Examiner rejected claims 5, 7, 9-10, and 16-18 under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter of the invention. The Examiner next rejected claims 1-4, 7, 9, and 11-14 under 35 U.S.C. § 102(b) as being anticipated by the article by Claudia Pfannschmidt et al. entitled Sequence-specific labeling of superhelical DNA by triple helix formation and psoralen crosslinking (Nucleic Acids Research, 1996, Vol. 24, No. 9, pages 1702-1709) ("Pfannschmidt"). Next, the Examiner rejected claims 1-3, 5-7, 9, and 11-14 under 35 U.S.C. § 103(a) over Pfannschmidt in view of US Patent 5,760,300 to Hiroshi Kajimura ("Kajimura"). Claims 1-4, 7, and 9-14 were rejected under § 103 over Pfannschmidt in view of US Patent 5,314,829 to L. Stephen Coles ("Coles") and claims 1-4, 7, 9, and 11-18 under § 103 over Pfannschmidt in view of US Patent 5,445,971 to Thomas E. Rohr ("Rohr").

Figure 1 has now been labeled to properly reflect the fact that it is Figure 1. Furthermore, the drawings have been further amended to comply with the Draftsperson's Patent Drawing Review.

Reconsideration of the pending claims is respectfully requested in view of the above amendments and the following comments.

I. The 35 U.S.C. § 112 Rejections Are Moot In Light Of The Above Amendments And the Following Remarks.

Claims 5, 7, 9, and 16-18 were each rejected under 35 U.S.C. § 112, second paragraph. Each of these claims have been amended to better point out and distinctly claim the subject matter which the applicant regards as the invention and to comply with the Examiner's rejections.

The Examiner rejected claim 10 as not being clear as to the relationship between creating a bar code and the analysis step. The Applicant would respectfully ask that the Examiner review the specification at page 17, lines 7-22, and in particular page 17, lines 19-22, for an explanation of how the bar codes are utilized in the present invention to help analyze the nucleic acid samples. It is believed that claim 10 is clear when read in light of this portion of the specification.

## II. Amended Claim 1 Is Not Anticipated By Pfannschmidt.

Claims 1-4, 7, 9, and 11-14 have been rejected by the Examiner as anticipated under 35 U.S.C. § 102(b). Since each of claims 2-4, 7, 9, and 11-14 depend directly or indirectly on independent claim 1, the allowability of these claims depends on the allowability of independent claim 1. The Applicant respectfully submits that, as amended, independent claim 1 is allowable over the Pfannschmidt reference cited by the Examiner. In order for Pfannschmidt to anticipate independent claim 1, each claimed element must be disclosed in the same. Independent claim 1, however, clearly points out novel features not taught or suggested by Pfannschmidt.

First, Pfannschmidt discloses a method of sequence specific labeling of supercoiled DNA by forming triple helices and psoralen photocrosslinking. The crosslink allows for covalent attachment to the DNA which survives at neutral pH's, thus rendering the biotin more accessible for binding by avidin or streptavidin. Pfannschmidt's states that "stoichiometric tagging of the crosslinked oligonucleotide is expected." Pfannschmidt, p. 1708. Put simply, the Pfannschmidt reference teaches the site-specific labeling of covalently closed circular DNA using triple helix-forming oligonucleotides.

In contrast, the present invention teaches a method of tagging two or more sequence specific sites of a nucleic acid sample, scanning the nucleic acid sample, and then analyzing the scan to determine the relative positions of the tagged sequence specific sites. The present invention teaches a method for utilizing a scanning probe microscope to determine the relative position of the tags, indicating the distance between the tagged sequences of the nucleic acid sample. The physical maps created using the present invention method allows for re-assembly of mapped DNA fragments into the correct order by aligning the tagged sections. The method of the present invention is clearly not taught or suggested by Pfannschmidt.

Second, the application of Pfannschmidt is limited by the fact that it specifically deals with triple helix DNA consisting of a single-stranded probe bound within the major groove of a double stranded target sequence. The "Strategy for site-specific labeling of supercoiled DNA" does not teach or suggest the elements of the claimed invention. Pfannschmidt, p. 1704.

Finally, the analysis step taught in Pfannschmidt does not teach or suggest measuring the distance between multiple tagged sequence specific sites.

### III. The 35 U.S.C. § 103(a) Rejections Based On Pfannschmidt In View Of Either Kajimura, Coles, Rohr Do Not Teach Or Suggest The Present Invention.

The Examiner next rejected all of the claims as being obvious under 35 U.S.C. § 103(a) over Pfannschmidt in view of Kajimura (claims 1-3, 5-7, 9, and 11-14), over Pfannschmidt in view of Coles (claims 1-4, 5, and 9-14), and over Pfannschmidt in view of Rohr (claims 1-4, 7, 9, and 11-18). Because dependent claims 2-7 and 9-18 depend on independent claim 1 either directly or indirectly, the arguments presented above regarding the allowability of independent claim 1 over Pfannschmidt apply *a fortiori* to these claims. As such, each of the dependent claims are patentable over Pfannschmidt. The additional art cited by the Examiner is only utilized to reject dependent claims that incorporate by reference all of the elements of independent claim 1. A few words about each of these references, however, may be helpful to

illustrate how they do not teach or suggest, alone or in combination with Pfannschmidt, all of the elements of the claimed invention.

Kajimura does teach that a near field optical microscope is the same or similar to an AFM or an STM and equivalent for many purposes. This is not disputed. It does not follow, however, that because these instruments may be equivalent for purposes of utilization in the present invention method, that Pfannschmidt teaches or suggests any more about the method as claimed in independent claim 1. The combination of Pfannschmidt and Kajimura does not teach or suggest tagging specific binding sites not measuring the distance between these sites.

The combination of Pfannschmidt and Coles also does not teach or suggest the claims of the present invention. The bar codes taught in Coles are used in a completely different manner than the bar codes of the present invention. The bar codes of the present invention are used as a graphical representation to help determine the distance between the tagged sequence specific sites of the nucleic acid samples. The bar codes in Coles are used to "permit the STM or AFM to scan across the substrate and then return to the originally imaged section of the grid for a repeat image." Coles, Col. 2, lns. 61-63. The bar codes in Coles are used as a street sign to indicate to the STM or AFM when it has returned to its starting point. The bar codes of Coles do not teach or suggest any measuring of the distances between the sites.

Finally, Rohr does suggest that a dipstick can be used "for a dip and read assay." Rohr, however, does not teach or suggest that a nucleic acid sample can be covalently tethered to the dipstick for use in a method as claimed in independent claim 1.

### CONCLUSION

In view of the above amendments and preceding remarks, Applicants respectfully urge that the Examiner's rejections be reconsidered and withdrawn, and that the pending claims be allowed. However, if the Examiner believes that any issues remain unresolved, he is invited to telephone the undersigned to expedite allowance.

Respectfully submitted,

Date: 8-9-01

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**MARKED-UP VERSION SHOWING CHANGES**

**IN THE CLAIMS**

1. (Amended) A method for analyzing a nucleic acid sample, the method comprising
  - (a) tagging two or more sequence specific sites of the nucleic acid;
  - (b) scanning the nucleic acid sample; and
  - (c) analyzing the scan of the nucleic acid sample to determine the relative positions of the tagged sequence specific sites of the nucleic acid.
5. (Amended) The method of claim 2 wherein said scanning step [the] further comprises utilizing a near field optical microscope.
7. (Amended) The method of claim 1 wherein said sequence-specific tag is chosen from one or more of the group [comprising] consisting of a [restriction endonuclease, a transcription factor, a modified nucleotide, a peptide, a nucleotide] nucleic acid, a protein, and a single molecule conjugated to a microparticle or a nanoparticle.
9. (Amended) The method of claim 1 wherein the nucleic acid sample is DNA chosen from one or more of the group [comprising] consisting of a cosmid, a bacterial artificial chromosome, and a yeast artificial chromosome.
16. (Amended) The method of claim 15 wherein the functional group is chosen from one or more of the group [comprising] consisting of biotin-avidin complexes, primary amines, sulphydryl groups, single stranded binding proteins, and histidine terminated oligonucleotides.
17. (Amended) The method of claim 16 wherein the deposition surface is [located] on a dipstick.

18. (Amended) The method of claim 17 wherein the deposition surface on the dipstick has specific areas for tethering different types of function group modified nucleic acid sequences.